9/29/04

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| NEWS | 2 | | "Ask CAS" for self-help around the clock |
| NEWS | 3 | Jul 12 | BEILSTEIN enhanced with new display and select options, resulting in a closer connection to BABS |
| NEWS | 4 | AUG 02 | IFIPAT/IFIUDB/IFICDB reloaded with new search and display fields |
| NEWS | 5 | AUG 02 | CAplus and CA patent records enhanced with European and Japan Patent Office Classifications |
| NEWS | 6 | AUG 02 | The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available |
| NEWS | 7 | AUG 27 | BIOCOMMERCE: Changes and enhancements to content coverage |
| NEWS | 8 | AUG 27 | BIOTECHABS/BIOTECHDS: Two new display fields added for legal status data from INPADOC |
| NEWS | 9 | SEP 01 | INPADOC: New family current-awareness alert (SDI) available |
| NEWS | 10 | SEP 01 | New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover! |
| NEWS | 11 | SEP 01 | New display format, HITSTR, available in WPIDS/WPINDEX/WPIX |
| NEWS | 12 | SEP 14 | STN Patent Forum to be held October 13, 2004, in Iselin, NJ |
| NEWS | 13 | SEP 27 | STANDARDS will no longer be available on STN |
| NEWS | 14 | SEP 27 | SWETSCAN will no longer be available on STN |

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| NEWS EXPRESS | JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004 |
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| NEWS INTER | General Internet Information |
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FILE 'HOME' ENTERED AT 14:29:44 ON 29 SEP 2004

10688348

9/29/04

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=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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STRUCTURE FILE UPDATES:   28 SEP 2004  HIGHEST RN 753424-73-6
DICTIONARY FILE UPDATES:  28 SEP 2004  HIGHEST RN 753424-73-6

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to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 14:30:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      0 TO ITERATE

100.0% PROCESSED       0 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=>  s l1 ful
FULL SEARCH INITIATED 14:30:19 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     19 TO ITERATE

100.0% PROCESSED      19 ITERATIONS                               14 ANSWERS
SEARCH TIME: 00.00.01

L3           14 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
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9/29/04

FULL ESTIMATED COST 155.42 155.63

FILE 'CAPLUS' ENTERED AT 14:30:22 ON 29 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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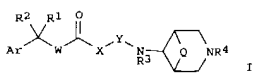
FILE COVERS 1907 - 29 Sep 2004 VOL 141 ISS 14
FILE LAST UPDATED: 28 Sep 2004 (20040928/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 24 L3

=> d abs bib hitstr 1-24

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB Title compds. [I; Ar = (substituted) aryl, heteroaryl; R1 = H, OH, HOCH2, alkyl, amino, alkoxy, cycloalkyl, carbamoyl, halo, aryl; R2 = alkyl, cycloalkyl, cycloalkenyl, (substituted) aryl, heteroaryl; W = (CH2)p; p = 0, 1; X = O, S, NR, null; Y = CHR5CO; R5 = H, Me, (CH2)q; q = 0-4; Q = (CH2)m; m = 0-2; R3 = H, alkyl, CO2CMe3; R4 = (unsatd.) (substituted) aliphatyl], were prepared Thus, 5-bromo-4-methylpent-3-ene, (1α,5α,6α)-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane, and K2CO3 were refluxed 5 h in MeCN to give (1α,5α,6α)-N-3 (4 methyl-3-pentenyl)-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane. This was treated with aqueous HCl in EtOAc at 0° to give (1α,5α,6α)-N-3-(4-methyl 3-pentenyl)-6-amino-3-azabicyclo[3.1.0]hexane. The latter was stirred with 2-hydroxy-2 cyclopentyl-2-(4-methoxyphenyl)acetic acid, hydroxybenzotriazole, N-methylmorpholine, and EDC.HCl in DMF at 0° to room temperature to give (1α,5α,6α)-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-hydroxy-2-cyclopentyl-2 (4-methoxyphenyl}acetamide. In a contractile assay using rat bladder strips, I showed pKB = 5.08-8.36 nM.
AN 2004:648506 CAPLUS
DN 141:190686
TI Preparation of 3,6 disubstituted azabicyclohexanes as muscarinic receptor antagonists
IN Mehta, Anita; Silamkoti, Arundutt V.; Kumar, Naresh; Gupta, Jang Bahadur
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

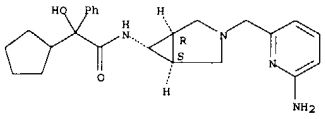
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2004067510 | A1 | 20040812 | WO 2003-IB256 | 20030128 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

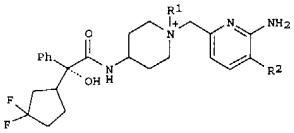
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
ML, MR, NE, SN, TD, TG
PRAI WO 2003-IB256 20030128
OS MARPAT 141:190686
IT **738628-36-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of 3,6 disubstituted azabicyclohexanes as muscarinic receptor antagonists)
RN 738628-36-9 CAPLUS
CN Benzeneacetamide, N-[(1α,5α,6α)-3-[(6-amino-2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hex-6-yl]-α-cyclopentyl-α-hydroxy- (9CI) (CA INDEX NAME)

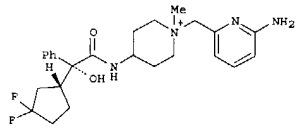
Relative stereochemistry.



L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II

AB Title compds. I•X- [wherein R1 = (un)substituted alkyl, CH2-alkenyl, CH2-alkynyl; R2 = H, OH; X = anion of a pharmaceutically acceptable acid such as tartaric, HCl, HBr, HI, H2SO4, H3PO4, HNO3, citric, methanesulfonic, benzoic, etc.; and any of their stereoisomers] were prepared as muscarinic receptor antagonists for treating asthma, chronic obstructive pulmonary disorder, allergic rhinitis, and infectious rhinitis. For example, II•I- was prepared by alkylation of the free piperidine with Me iodide in toluene/acetonitrile overnight at 20-25°. Six clin. examples are given. For instance II•I improved the peak flow from 5 l/s to 9 l/s after a week of its administration to a 35 yr old male as a powder at 100 μM once a day.
AN 2004:387264 CAPLUS
DN 140:406738
TI Preparation of quaternary ammonium compounds, in particular piperidinium derivatives, as muscarinic receptor antagonists
IN Heath, Timothy Gordon
PA Pharmacia & Upjohn Company, USA
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2004039374 | A1 | 20040513 | WO 2003-IB4617 | 20031017 |

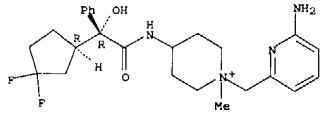
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004132774 A1 20040708 US 2003-688348 20031017
PRAI US 2002-421962P P 20021029
OS MARPAT 140:406738
IT **688320-38-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(muscarinic receptor antagonist; preparation of quaternary ammonium compds., in particular piperidinium derivs., as muscarinic receptor antagonists)
RN 688320-38-9 CAPLUS
CN Piperidinium, 1-[(6-amino-2-pyridinyl)methyl]-4-[[(2R)-[(1R)-3,3-difluorocyclopentyl]hydroxyphenylacetyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

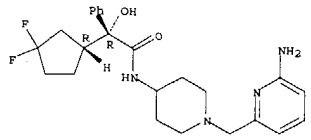


● I-

IT **203321-88-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quaternary ammonium compds., in particular piperidinium derivs., as muscarinic receptor antagonists)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB The possible mechanisms for the chiral recognition of 2-(R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2 phenylacetamide (RR-M3), and its enantiomer (SS-M3) with octakis(2,3-di-O-acetyl-6-sulfo)-γ-cyclodextrin (ODAS-γ-CD) and octakis(6-sulfo)-γ-cyclodextrin (OS γ-CD), were studied using capillary electrophoresis (CE), proton (1H), fluorine (19F) and carbon (13C) NMR spectroscopy (NMR), and IR spectroscopy. Clear evidence for the formation of diastereomeric complexes between the enantiomers and the two CDs was observed. NMR spectra suggest that the Ph and difluorocyclopentyl rings are involved in the complexation. The Ph ring on the guest mol. is deeply penetrated into the cavity of OS-γ-CD, but it is not included into the cavity of ODAS-γ-CD. The continuous variation plots built based on the 1H NMR and IR spectra indicate a 1:1 complex stoichiometric ratio of the M3 enantiomers for both CDs. The affinity of the enantiomers for the two CDs is opposite.

AN 2003:684003 CAPLUS

DN 139:373801

TI Mechanistic study of the enantiomeric recognition of a basic compound with negatively charged single-isomer γ-cyclodextrin derivatives using capillary electrophoresis, nuclear magnetic resonance spectroscopy, and infrared spectroscopy

AU Zhou, Lili; Thompson, Richard; Reamer, Robert A.; Lin, Zhihao; French, Mike; Ellison, Dean; Wyvratt, Jean

CS Merck Research Laboratories, Rahway, NJ, USA

SO Electrophoresis (2003), 24(15), 2448-2455
CODEN: ELCTDN; ISSN: 0173-0835

PB Wiley-VCH Verlag GmbH & Co. KGaA

DT Journal

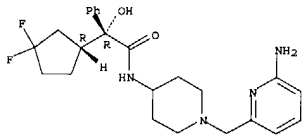
LA English

IT **203321-88-4 476478-92-9**
RL: ANT (Analyte); ANST (Analytical study)
(capillary electrophoresis, NMR and IR spectroscopy in mechanistic study of enantiomeric recognition of aminopyridinylmethylpiperidine acetamide derivative using neg. charged single-isomer γ-cyclodextrin derivs.)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

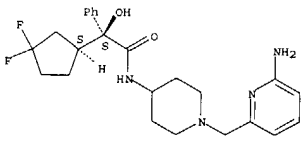


L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RN 476478-92-9 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1S)-3,3-difluorocyclopentyl]-α-hydroxy-, (αS)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB To investigate whether the inhibition of muscarinic M2 receptors results in the enhancement of reflex bronchoconstriction under airway hyperresponsiveness, we evaluated the effects of muscarinic antagonists with or without M2 antagonist activity on methacholine (MCh)- and SO2-induced airway responses in ovalbumin (OVA) sensitized and -challenged mice. In this model, similar airway hyperresponsiveness to MCh (12 mg/mL) was observed on Days 31 and 37 (2.2-fold and 2.7-fold, resp.). However, airway hyperresponsiveness to SO2 (0.05 l/min) on Day 37 was less than that on Day 31 (4.0- and 2.7-fold on Days 31 and 37), indicating reflex bronchoconstriction was enhanced on Day 31 in comparison to Day 37. Ipratropium (0.03 - 0.3 mg/mL, inhalation) and Compound A (0.1 - 3 mg/kg, p.o.) inhibited MCh-induced responses on Days 31 and 37. Although ipratropium (0.03 - 1 mg/mL) dose-dependently inhibited SO2-induced responses on Day 31, ipratropium at a dose of 0.1 mg/mL significantly increased SO2-induced responses on Day 37 (162.2% of the corresponding control). On the other hand, Compound A (0.03 - 0.3 mg/kg, p.o.) inhibited SO2-induced responses without any increases on Days 31 and 37. These results suggest that two different conditions of reflex bronchoconstriction are presented in this model: SO2-induced responses are enhanced by dysfunctional M2 receptors on Day 31 while the dysfunctional M2 receptors are partially restored on Day 37. In addition, the inhibition of the restored M2 receptors further enhance reflex bronchoconstriction.

AN 2003:598944 CAPLUS

DN 140:613

TI Effects of muscarinic receptor antagonists with or without M2 antagonist activity on cholinergic reflex bronchoconstriction in ovalbumin-sensitized and -challenged mice

AU Hirose, Hiroyasu; Jiang, Jian; Nishikibe, Masaru

CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Tsukuba, 300-2611, Japan

SO Journal of Pharmacological Sciences (Tokyo, Japan) (2003), 92(3), 209-217
CODEN: JPSTGJ; ISSN: 1347-8613

PB Japanese Pharmacological Society

DT Journal

LA English

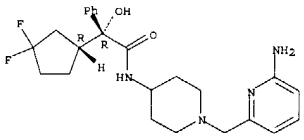
IT **203321-88-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of muscarinic receptor antagonist activity on cholinergic reflex bronchoconstriction)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

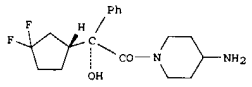
Absolute stereochemistry. Rotation (+).

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI

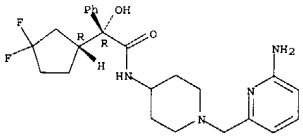


I

AB Title compds. carrying a variety of diamine moieties without hydrophobic substituent on the nitrogen atom were screened against the binding affinity for the M3 receptor and the selectivity for M3 over the M1 and M2 receptors. This process led to a 4-aminopiperidinamide (I) with a Ki value of 5.1 nM and with a selectivity of the M3 receptor that was 46-fold greater than that of the M2 receptor. Further derivatization of I by inserting a spacer group or by incorporating alkyl group(s) into the amine part resulted in the identification of an 4-(aminoethyl)piperidinamide with a Ki value of 3.7 nM for the M3 receptor and a selectivity for the M3 receptor that was 170-fold greater than that of the M2 receptor.
AN 2003:442757 CAPLUS
DN 139:173181
TI Muscarinic M3 receptor antagonists with (2R)-2-[(1R)-3,3-Difluorocyclopentyl] 2 hydroxyphenylacetamide structures. Part 2
AU Ogino, Yoshio; Ohtake, Norikazu; Kobayashi, Kensuke; Kimura, Toshifumi; Fujikawa, Toru; Hasegawa, Takuro; Noguchi, Kazuhito; Mase, Toshiaki
CS Banyu Tsukuba Research Institute (Collaboration with Merck Research Laboratories), Tsukuba, Ibaraki, 300-2611, Japan
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(13), 2167-2172
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
OS CASREACT 139:173181
IT **203321-88-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of fluorocyclopentyl hydroxyphenylacetamides as muscarinic M3 receptor antagonists)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl] α-hydroxy-, (αR)- (9CI)

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(CA INDEX NAME)

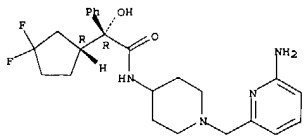
Absolute stereochemistry. Rotation (+).



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB A review on discussing development of synthetic process for a muscarine M3 receptor antagonist through diastereoselective Michael reaction, selective deoxyfluorination and aromatic metal-halogen exchange reaction, etc.
AN 2003:177129 CAPLUS
DN 139:307641
TI Development of manufacturing process of muscarine M3 receptor antagonist
AU Iida, Takehiko; Mase, Toshiaki
CS Lab. for Synthetic Technology, Banyu Pharmaceutical Co., Ltd., Japan
SO Purosesu Kemisutori no Shintenkai (2003), 238-252 Publisher: Shi Emu Shi Shuppan, Tokyo, Japan.
CODEN: 69DQZN; ISBN: 4-88231-384-7
DT Conference; General Review
LA Japanese
IT **203321-88-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(development of manufacturing process of muscarine M3 receptor antagonist)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl] 4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB The simultaneous enantiosepn. of a basic drug compound, 2(R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl] 2-hydroxy 2-phenylacetamide (M3), and its chiral acidic intermediate, (R,R) 1-(2,2-difluorocyclopentyl)-phenylacetic acid (MA), was investigated by capillary electrophoresis (CE) with various cyclodextrins (CDs). After an initial screening, a single-isomer CD, octakis(2,3-diacetyl-6-sulfo)-gamma-CD (ODAS-γ-CD), was selected for further method development based on separation selectivity and the peak migration time. Other method parameters such as pH of background electrolyte (BGE), type of capillary, temperature, and organic modifier were varied to optimize the method. The optimal method was validated in terms of linearity, sensitivity, precision, ruggedness, and specificity. A mixture of enantiomers of M3 and MA were spiked into a matrix of reagents used for the synthetic step and the resulting solution was evaluated by the optimized CE-chiral method. The results indicate both pairs of M3 and MA enantiomers were free of interference from the reaction matrix. Therefore, the feasibility of utilizing the method to monitor possible enantio-conversion during the synthetic process was demonstrated.

AN 2003:11675 CAPLUS

DN 139:202627

TI Simultaneous enantioseparation of a basic drug compound and its acidic intermediate by capillary electrophoresis

AU Zhou, Lili; Thompson, Richard; French, Mike; Ellison, Dean; Wyvratt, Jean

CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA

SO Journal of Separation Science (2002), 25(15-17), 1183-1189
CODEN: JSSCCJ; ISSN: 1615 9306

PB Wiley-VCH Verlag GmbH & Co. KGaA

DT Journal

LA English

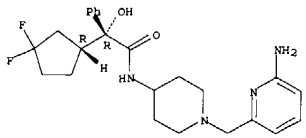
IT **203321-88-4**
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous enantiosepn. of a basic drug compound and its acidic intermediate by CE)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R) 3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB The enantiosepn. of a weakly basic pharmaceutical drug substance was investigated using sulfated-β-CD as a chiral selector. The enantiomers are separated at acidic pHs in an anodic flow due to complexation with sulfated-β-CD, while under an electroosmotic flow (EOF) counter-current. At basic pHs, the EOF prevails and the analytes migrate toward the cathode, where improved sepns. can be obtained along with an apparent reversal of migration order. The optimal enantiosepn. of the test compound was systematically explored by varying important factors, such as pH, concentration of sulfated-β-CD, temperature, and addition of organic modifier.
The implications of the results on general enantiosepn. of weakly basic pharmaceutical compds. were discussed.

AN 2002:942501 CAPLUS

DN 139:90581

TI Enantiomeric separation of a drug substance using capillary electrophoresis with sulfated-β cyclodextrin

AU Yuan, Huimin; Thompson, Richard A.; Ellison, Dean K.

CS Analytical Research Department, Merck Research Laboratories, Merck and Co., Inc., Rahway, NJ, 07065, USA

SO Journal of Liquid Chromatography & Related Technologies (2002), 25(19), 2999-3015
CODEN: JLCTFC; ISSN: 1082-6076

PB Marcel Dekker, Inc.

DT Journal

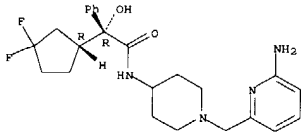
LA English

IT **203321-88-4 476478-92-9**
RL: ANT (Analyte); ANST (Analytical study)
(enantiomeric separation of J-104129 pyridinyl difluorocyclopentyl derivative by capillary electrophoresis using sulfated-β-cyclodextrin as chiral selector)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

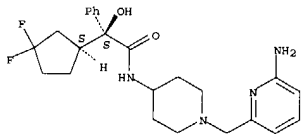


RN 476478-92-9 CAPLUS

CN Benzeneacetamide, N-[1 [(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1S)-3,3-difluorocyclopentyl]-α hydroxy-, (αS)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB Male rats were treated with a muscarinic receptor antagonist at 3, 10, and 100 mg/kg/day for 4 wk prior to mating with untreated females and their reproductive status was determined on gestation days (GD) 15-17. Treatment-related decreases in the pregnancy rate were observed at 100 mg/kg/day without any effects on mating performance. Impairment of male fertility by this compound was also observed after treatment for 1 wk, but there were no effects after a 1-wk withdrawal period suggesting reversibility of the effect. There were no treatment-related effects on sperm production or motility, or testicular histopathol. in any group. In order to determine whether the reduced fertility was a class effect of muscarinic receptor antagonists, atropine was examined. Males received atropine for 1 wk at 62.5 and 125 mg/kg/day and were mated with untreated females. A low pregnancy rate associated with a decrease in the number of implantations was observed at 125 mg/kg/day. The effect on implantation was also observed at 62.5 mg/kg/day. These findings suggest that the impairment of fertility in male rats induced by muscarinic receptor antagonists is a class effect, and has a relatively short onset of effect and is quickly reversible.

AN 2002:804224 CAPLUS

DN 138:395946

TI Impairment of male fertility induced by muscarinic receptor antagonists in rats

AU Ban, Yoshiki; Sato, Takahiro; Nakatsuka, Toshio; Kemi, Masayuki; Samura, Keiji; Matsumoto, Hiroyoshi; Cukierski, Mark A.; van Zwieten, Matthew J.

CS Safety Assessment, Banyu Pharmaceutical Co., Ltd., Menuma-machi, Osato-gun, Saitama, 360-0214, Japan

SO Reproductive Toxicology (2002), 16(6), 757-765
CODEN: REPTED; ISSN: 0890-6238

PB Elsevier Science Inc.

DT Journal

LA English

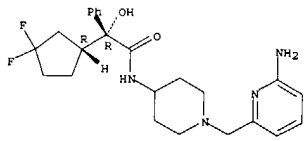
IT **203321-88-4**
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(impairment of male fertility induced by muscarinic receptor antagonists)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl] α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB The authors evaluated in vivo functional selectivity profiles for muscarinic M2 and M3 subtypes of four muscarinic antagonists: Compound A (a novel muscarinic receptor antagonist with M2-sparing antagonistic activity), darifenacin, (a muscarinic M3 receptor antagonist); methoctramine (a muscarinic M2 receptor antagonist) and tolterodine (a nonselective muscarinic receptor antagonist), and compared the inhibition potency on distention-induced bladder contraction in rats. In an in vivo functional study, Compound A (0.03-10 mg/kg, i.v.) showed antimuscarinic activity with high selectivity for M3 (salivation) over M2 (bradycardia) (>100-fold). Darifenacin (0.01-0.3 mg/kg, i.v.) showed only slight selectivity for M3 over M2 (3.7 fold). Methoctramine (0.003-1 mg/kg, i.v.) showed the reverse selectivity profile (0.077-fold). Tolterodine (0.003-0.3 mg/kg, i.v.) showed less selectivity (1.2-fold). Compound A at M3 inhibitory doses (0.1 and 0.3 mg/kg, i.v.) showed inhibition in a distention-induced neurogenic bladder contraction model, and its maximal inhibitory effects were about 60% at an even higher dose (3 mg/kg). Methoctramine at M2 inhibitory doses (0.03 and 0.1 mg/kg, i.v.) did not significantly affect distention-induced bladder contraction. When tolterodine and darifenacin caused inhibition of distention-induced bladder contraction, its maximal inhibitory effects were similar to that of Compound A. Therefore, these findings suggest that Compound A would be an excellent pharmacol. tool to give a better understanding of which subtypes of muscarinic receptors act in bladder function so far, and muscarinic M3, but not M2, receptors mainly mediate the cholinergic component of distention-induced bladder contraction.

AN 2002:725247 CAPLUS

DN 138:66945

TI The subtypes of muscarinic receptors for neurogenic bladder contraction in rats

AU Hirose, Hiroyasu; Aoki, Ikuo; Kimura, Toshifumi; Fujikawa, Toru; Numazawa, Tomoshige; Sasaki, Kaori; Nishikibe, Masaru; Noguchi, Kazuhito

CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Ibaraki, Tsukuba, 300-2611, Japan

SO European Journal of Pharmacology (2002), 452(2), 245-253
CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier Science B.V.

DT Journal

LA English

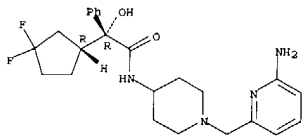
IT **203321-88-4**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(muscarinic receptors subtypes for neurogenic bladder contraction in rat)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6 amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR) (9CI)
(CA INDEX NAME)

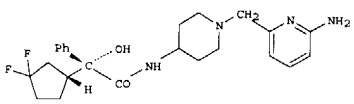
Absolute stereochemistry. Rotation (+).

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI

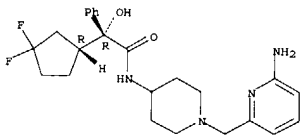


I

AB The purpose of the following investigation was to display the utility of 19F solid state NMR in both distinguishing between solid forms of a selective muscarinic M3 receptor antagonist (I) and characterizing the active pharmaceutical ingredient in low-dose tablets. Ambient- and elevated-temperature solid-state 19F fast (15 kHz) magic-angle spinning (MAS) NMR expts. were employed to obtain desired spectral resolution in this system. Ambient sample temperature combined with rotor frequencies of 15 kHz provided adequate 19F peak resolution to successfully distinguish crystalline and amorphous forms in this system. Addnl., elevated-temperature 19F MAS NMR further characterized solid forms through 19F resonance narrowing brought about by the phenomenon of solvent escape. Similar solvent dynamics at elevated temps. were utilized in combination with ambient-temperature 19F MAS NMR anal. to provide excipient-free spectra to unambiguously identify the active pharmaceutical ingredient (API) conversion from crystalline Form I to the amorphous form in low dose tablets. It is shown that 19F solid-state NMR is exceptionally powerful in distinguishing amorphous and crystalline forms in both bulk and formulation samples.

AN 2002:501965 CAPLUS
DN 138:243022
TI 19F solid-state NMR spectroscopic investigation of crystalline and amorphous forms of a selective muscarinic M3 receptor antagonist, in both bulk and pharmaceutical dosage form samples
AU Wenslow, Robert M.
CS Merck Research Laboratories, Merck and Co., Rahway, NJ, 07065-0900, USA
SO Drug Development and Industrial Pharmacy (2002), 28(5), 555-561
CODEN: DDIPD8; ISSN: 0363-9045
PB Marcel Dekker, Inc.
DT Journal
LA English
IT **203321-88-4**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(19F solid-state NMR spectroscopic investigation of cryst. and amorphous forms of muscarinic M3 receptor antagonist)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

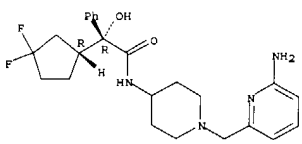


RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB The chiral separation of an M3 antagonist was investigated using capillary electrophoresis (CE) with various sulfated cyclodextrins and by reversed-phase liquid chromatog. with derivatized cellulose, derivatized amylose, and two protein stationary phases. Operational parameters for each technique, such as the concentration of the chiral selectors, background electrolyte (or mobile phase) pH and type, organic modifiers, injection mode and temperature were varied in order to achieve a desired elution order and to meet a 0.1% limit of quantitation (LOQ) criteria. Based on the advantages and disadvantages of each technique, a practical CE method using sulfated γ-cyclodextrin was selected. The method was validated in terms of linearity, LOQ, accuracy, ruggedness and precision.

AN 2002:417481 CAPLUS
DN 138:8443
TI Comparison of capillary electrophoresis and reversed-phase liquid chromatography for determination of the enantiomeric purity of an M3 antagonist
AU Song, S.; Zhou, L.; Thompson, R.; Yang, M.; Ellison, D.; Wyvratt, J. M.
CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA
SO Journal of Chromatography, A (2002), 959(1-2), 299-308
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier Science B.V.
DT Journal
LA English
IT **203321-88-4 476478-92-9**
RL: ANT (Analyte); ANST (Analytical study)
(determination of enantiomeric purity of an M3 antagonist by capillary electrophoresis and reversed-phase liquid chromatog.)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

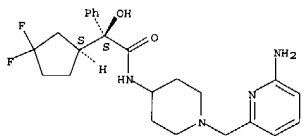
Absolute stereochemistry. Rotation (+).



RN 476478-92-9 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1S)-3,3-difluorocyclopentyl]-α-hydroxy-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB Investigations on compound A, an M2-sparing M3 muscarinic receptor antagonist, showed that focal polar anterior subcapsular lenticular opacities, characterized by focal epithelial proliferation, developed in Sprague-Dawley rats. The incidence and bilateral localization of this change increased generally with dose and time, though plateauing after 8 mo of treatment; however the severity progressed very slightly. Over a 1-yr period, no anterior cortical lens fiber changes or other histol. ocular changes developed. A decreased severity of the change and apoptosis suggested some regression after a 26-wk recovery period. Two nonselective muscarinic receptor antagonists, atropine and tolterodine, induced similar lenticular changes in rats. A hypothesis in relation to an indirect effect of the drug, such as increased illumination of the lens due to mydriasis observed with all these compds., was investigated and disproven. Because these opacities are induced by structurally unrelated muscarinic receptor antagonists (atropine and tolterodine), it is likely that these lenticular changes are the result of muscarinic receptor inhibition. However, hypotheses regarding a direct effect of the drug on muscarinic receptors in the lens epithelium, possibly mediated by drug and/or metabolite(s) in the aqueous humor and/or lens epithelium, remain to be investigated. This lenticular opacity is similar to that observed spontaneously in Sprague-Dawley rats, although the latter occur at a lower incidence. No such lenticular opacities have been reported in other animal species, including man, after treatment with muscarinic receptor antagonists.

AN 2002:203384 CAPLUS

DN 137:41691

TI Muscarinic receptor antagonist-induced lenticular opacity in rats

AU Durand, Genevieve; Hubert, Marie-Francoise; Kuno, Hiroshi; Cook, William O.; Boussiquet-Leroux, Christine; Owen, Roger; Fujimaki, Yukio; Kemi, Masayuki; Virat, Michel; Van Zwieten, Matthew J.

CS Laboratoires Merck Sharp and Dohme-Chibret, Clennont-Ferrand, 63963, Fr.

SO Toxicological Sciences (2002), 66(1), 166-172
CODEN: TOSCF2; ISSN: 1096-6080

PB Oxford University Press

DT Journal

LA English

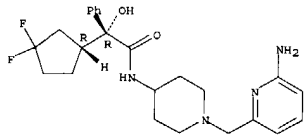
IT **203321-88-4**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(muscarinic receptor antagonist-induced lenticular opacity in rats)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl] α-[(1R)-3,3-difluorocyclopentyl] α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB A sensitive, specific, and robust liquid chromatog. (LC)/mass spectrometry (MS)/MS method was developed and validated for a novel M3 muscarinic receptor antagonist (I) and its active 5-OH metabolite (II) in human plasma. The assay involves a two-step liquid liquid extraction of the compds. from human plasma, HPLC separation, and MS/MS for the detection of the analytes. The method provides a linear response from a quantitation limit of 0.05-20 ng/mL for I and 0.1-20 ng/mL for II using 1 mL of plasma. The mean absolute recovery was 85.4% for I and 80.8% for II, resp. The intra-assay accuracy of I and II averaged from 95.0 to 105.3% with coefficient of variation (CV) values ≤6.5% over the standard curve range. The stability study showed that I and II are stable in the plasma matrix over a period of 11 mo at -70°. The accuracy, ruggedness, and reproducibility of this method were demonstrated by analyzing over 5000 plasma samples in clin. pharmacokinetics studies over a 6-mo period.

AN 2002:89423 CAPLUS

DN 137:134

TI Simultaneous determination of a novel M3 muscarinic receptor antagonist and its active 5-OH metabolite in human plasma using liquid chromatography/tandem mass spectrometry

AU Yan, Kerri X.; Song, Hengchang; Riffel, Kerry; Lo, Man-Wai

CS Department of Drug Metabolism, Merck Research Laboratories, West Point, PA, 19486, USA

SO Journal of Pharmaceutical and Biomedical Analysis (2002), 27(5), 699-709
CODEN: JPBADA; ISSN: 0731-7085

PB Elsevier Science B.V.

DT Journal

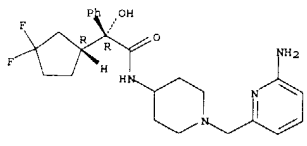
LA English

IT **203321-88-4 433211-57-5**
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous determination of a novel M3 muscarinic receptor antagonist and its active 5-OH metabolite in human plasma using liquid chromatog./tandem mass spectrometry)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

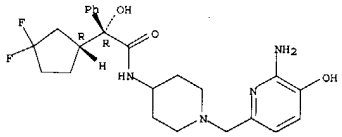


L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RN 433211-57-5 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-5-hydroxy-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB Enantiosepns. of basic pharmaceutical compds. were investigated using different types of sulfated cyclodextrins as chiral selectors. A general strategy for method development was described, together with enantiomeric sepns. of a number of pharmaceutical related compds. Based on this strategy, systematic method development approaches for several selected compds. were performed by modifying method parameters, such as the concentration of the chiral selectors, buffer pH, type of organic modifiers, buffer type, temperature and applied voltage. The results of the investigation elucidated the separation mechanism. Many practical aspects were also discussed through several specific examples in order to demonstrate how to develop and validate a precise, sensitive, accurate and rugged separation

AN 2002:2310 CAPLUS

DN 136:406973

TI A strategic approach to the development of capillary electrophoresis chiral methods for pharmaceutical basic compounds using sulfated cyclodextrins

AU Zhou, Lili; Thompson, Richard; Song, Sherry; Ellison, Dean; Wyvratt, Jean M.

CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA

SO Journal of Pharmaceutical and Biomedical Analysis (2001), Volume Date 2002, 27(3-4), 541-553
CODEN: JPBADA; ISSN: 0731 7085

PB Elsevier Science B.V.

DT Journal

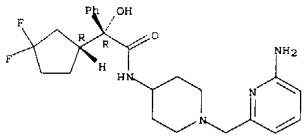
LA English

IT **203321-88-4**
RL: ANT (Analyte); ANST (Analytical study)
(strategic approach to development of capillary electrophoresis chiral methods for pharmaceutical basic compds. using sulfated cyclodextrins)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB An improved and efficient synthesis for the preparation of 2-amino-6-[(4-aminopiperidin-1-yl)methyl]pyridine, an intermediate compound in the preparation of muscarinic M3 receptor antagonists, includes as a final step the removal of trimethylacetyl and an amino protecting group from 2-trimethylacetyl-amino 6-[(4-protected aminopiperidin-1-yl)methyl]pyridine. Also prepared was (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.

AN 2001:906225 CAPLUS

DN 136:37520

TI Process for the preparation of piperidine derivatives

IN Maligres, Peter E.; Lee, Jaemoon

PA USA

SO U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI US 2001051727 | A1 | 20011213 | US 2001-799440 | 20010305 |
| US 6469172 | B2 | 20021022 | | |
| PRAI US 2000-187816P | P | 20000308 | | |

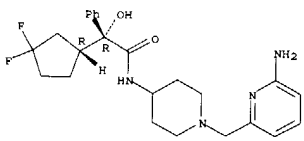
OS CASREACT 136:37520; MARPAT 136:37520

IT **203321-88-4P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of piperidine derivs.)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

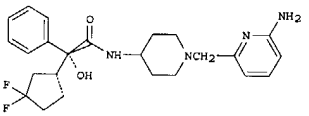
Absolute stereochemistry. Rotation (+).



L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB An efficient synthesis of a structurally unique, novel M3 antagonist I is described. I is conveniently disconnected retrosynthetically at the amide bond to reveal the acid portion and the amine fragment. The synthesis of the acid key intermediate is highlighted by a ZnCl2-MABP complex catalyzed diastereoselective Michael reaction of a dioxolane with 2-cyclopenten-1-one to establish the contiguous quaternary tertiary chiral centers and a subsequent geminal difluorination of a ketone using Deoxofluor in the presence of catalytic BF3·OEt2. The synthesis of the amine moiety is highlighted by the discovery of a novel n-Bu3MgLi magnesium-halogen exchange reaction for selective functionalization of 2,6-dibromopyridine. This new and practical metalation protocol obviated cryogenic conditions and upon quenching with DMF gave 6-bromo-2-formylpyridine in excellent yield. Further transformations afforded the amine fragment via reductive amination, Pd-catalyzed aromatic amination, and deprotection. Finally, the highly convergent synthesis of I was accomplished by coupling of the two fragments. This synthesis has been used to prepare multi-kilogram quantities of the bulk drug.

AN 2001:653072 CAPLUS

DN 135:357830

TI Synthesis of a Muscarinic Receptor Antagonist via a Diastereoselective Michael Reaction, Selective Deoxyfluorination and Aromatic Metal-Halogen Exchange Reaction

AU Mase, Toshiaki; Houpis, Ioannis N.; Akao, Atsushi; Dorziotis, Iliias; Emerson, Khateeta; Hoang, Thoa; Iida, Takehiko; Itoh, Takahiro; Kamei, Keisuke; Kato, Shinji; Kato, Yoshiaki; Kawasaki, Masashi; Lang, Fengrui; Lee, Jaemoon; Lynch, Joseph; Maligres, Peter; Molina, Audrey; Nemoto, Takayuki; Okada, Shigemitsu; Reamer, Robert; Song, Jake Z.; Tschaen, David; Wada, Toshihiro; Zewge, Daniel; Volante, R. P.; Reider, Paul J.; Tomimoto, Koji

CS Process R & D Laboratories for Technology Development, Banyu Pharmaceutical Co. Ltd., Okazaki Aichi, 444-0858, Japan

SO Journal of Organic Chemistry (2001), 66(20), 6775-6786
CODEN: JOCEAH; ISSN: 0022-3263

PB American Chemical Society

DT Journal

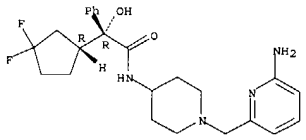
LA English

OS CASREACT 135:357830

IT **203321-88-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of muscarinic receptor antagonist via a diastereoselective

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
Michael reaction, selective deoxyfluorination and arom. metal-halogen exchange reaction)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

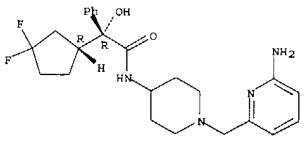


RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB The pharmacol. profiles of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (I), which is a novel muscarinic receptor antagonist with M2-sparing antagonistic activity, was evaluated. I inhibited [3H]NMS binding to cloned human muscarinic m1, m2, m3, m4, and m5 receptors expressed in Chinese hamster ovary cells with Ki values (nM) of 1.5, 540, 2.8, 15, and 7.7, resp. In isolated rat tissues, I inhibited carbachol-induced responses with 540-fold selectivity for trachea (KB = 1.2 nM) over atria (KB = 650 nM). In in vivo rat assays, I inhibited acetylcholine-induced bronchoconstriction and bradycardia with i.v. ED50 values of 0.022 and ≤10 mg/kg, resp. Furthermore, in dogs, I (0.1-1 mg/kg p.o.) dose dependently shifted the methacholine concentration-respiratory resistance curves. In mice, I (10 mg/kg i.v.) did not inhibit oxotremorine induced tremor. The brain/plasma ratio (KP) of I (3 mg/kg i.v.) was 0.13 in rats; this KP was less than scopolamine (1.7) and darifenacin (0.24). The inhibition of I (3 mg/kg i.v.) on ex vivo binding in rat cerebral cortex was almost similar to that of NMS. Therefore, I has high selectivity for M3 receptors over M2 receptors, displays a potent, oral M3 antagonistic activity without inhibition of central muscarinic receptors because of low brain penetration. It is well known that central muscarinic antagonists may have diverse CNS effects, and M2 receptors regulate cardiac pacing and act as autoreceptors in the lung and bladder. Thus, I may have fewer cardiac or CNS side effects than nonselective compds.
AN 2001:321650 CAPLUS
DN 135:132311
TI Pharmacological properties of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide: a novel muscarinic antagonist with M2-sparing antagonistic activity
AU Hirose, Hiroyasu; Aoki, Ikuo; Kimura, Toshifumi; Fujikawa, Toru; Numazawa, Tomoshige; Sasaki, Kaori; Sato, Akio; Hasegawa, Takuro; Nishikibe, Masaru; Mitsuya, Morihiro; Ohtake, Norikazu; Mase, Toshiaki; Noguchi, Kazuhito
CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Ibaraki, Japan
SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(2), 790-797
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
IT **203321-88-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(pharmacol. properties of, as novel muscarinic antagonist with M2-sparing antagonistic activity)

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

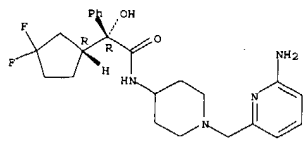
L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB A medical condition in men known as Lower Urinary Tract Symptoms (LUTS) is treated by the administration of a muscarinic receptor antagonist in combination with at least one of a 5α reductase inhibitor and an α-adrenergic receptor blocker.
AN 2001:228701 CAPLUS
DN 134:247264
TI Treatment of lower urinary tract symptoms with muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors, and pharmaceutical compositions for use therein
IN Stoner, Elizabeth; Drake, Paul J.; Bach, Mark A.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
PAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2001021167 | A1 | 20010329 | WO 2000-US25534 | 20000918 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-155357P P 19990922
OS MARPAT 134:247264
IT **203321-88-4 331412-18-1 331412-19-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors for treatment of lower urinary tract symptoms, and pharmaceutical compns.)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 331412-18-1 CAPLUS

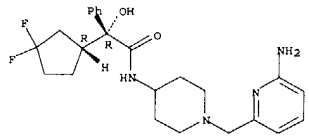
L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 1H-Indeno[5,4-f]quinoline-7-carboxamide, N-(1,1-dimethylethyl)-

2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-4a,6a-dimethyl-2-oxo-, (4aR,4bS,6aS,7S,9aS,9bS,11aR)-, mixt. with (αR)-N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl] α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxybenzeneacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 203321-88-4
CMF C24 H30 F2 N4 O2

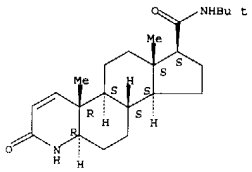
Absolute stereochemistry. Rotation (+).



CM 2

CRN 98319-26-7
CMF C23 H36 N2 O2

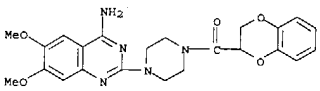
Absolute stereochemistry.



RN 331412-19-2 CAPLUS
CN 1H-Indeno[5,4-f]quinoline-7-carboxamide, N-(1,1-dimethylethyl)-

2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-4a,6a-dimethyl-2-oxo-, (4aR,4bS,6aS,7S,9aS,9bS,11aR)-, mixt. with 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazine and (αR)-N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



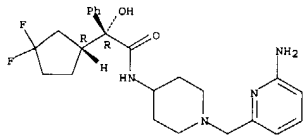
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
3,3-difluorocyclopentyl]-α-hydroxybenzeneacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 203321-88-4
CMF C24 H30 F2 N4 O2

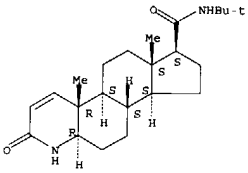
Absolute stereochemistry. Rotation (+).



CM 2

CRN 98319-26-7
CMF C23 H36 N2 O2

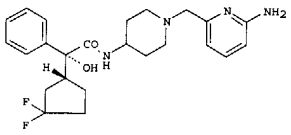
Absolute stereochemistry.



CM 3

CRN 74191-85-8
CMF C23 H25 N5 O5

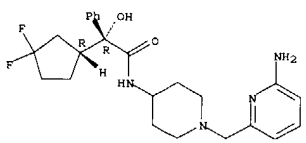
L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB Diastereoselective synthesis of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, a subunit of a novel muscarinic M3 receptor antagonist I (no biol. data presented), was achieved via Michael addition of an enolate of (2R,5R)-2-tert-butyl-5-phenyl-1,3-dioxolan-4-one to (-)-(3aS,4R,7S,7aR)-3a,4,7,7a-tetrahydro-4,7-methano-1H-inden-1-one in 90% de as a key step.
AN 2000:854212 CAPLUS
DN 134:207688
TI Diastereoselective Synthesis of the Acid Part of a New Muscarinic M3 Receptor Antagonist
AU Mitsuya, M.; Ogino, Y.; Ohtake, N.; Mase, T.
CS Banyu Tsukuba Research Institute in Collaboration with Merck Research Laboratories, Tsukuba, Ibaraki, 300-2611, Japan
SO Tetrahedron (2000), 56(51), 9901-9907
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 134:207688
IT **203321-88-4P**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(diastereoselective prepn of the benzeneacetamide subunit of a new muscarinic M3 receptor antagonist via stereoselective Michael addition and a retro Diels-Alder reaction)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

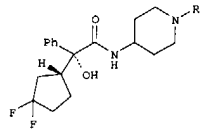
Absolute stereochemistry. Rotation (+).



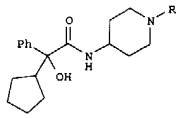
L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

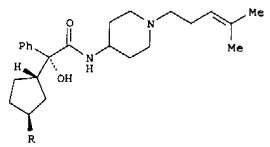
L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II



III

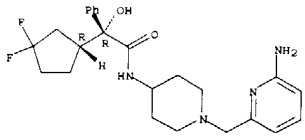
AB A novel series of (2R)-2-[(1R)-3,3-difluorocyclopentyl] 2-hydroxy-2-phenylacetamides I (R = CH2Ph, 3-furylmethyl, 2-pyridyl, etc.) and II (R = 2-MeC6H4CH2, cyclohexylmethyl, 3-pyridylmethyl, etc.) was designed and synthesized based on the structure and biol. profiles of an active metabolite III (R = OH) of the prototype muscarinic M3 receptor selective antagonist III (R = H), to develop a potent, long-acting, orally active M3 antagonist for the treatment of urinary tract disorders, irritable bowel syndrome, and respiratory disorders. Investigation of I [R = (substituted phenyl)methyl, (substituted pyridyl)methyl, (substituted thienyl)methyl] containing a Ph or heterocyclic ring as the piperidinyl side chain in place of the 4 methyl-3-pentenyl moiety of I (R = 4-Me-3-pentenyl) revealed that this acid moiety was a versatile template for improving the selectivity for M3 over M2 receptors in comparison with the corresponding cyclopentylphenylacetic acid group. However, since the in vitro metabolic stability of these analogs was insufficient compared with that of III (R = OH), further derivatization was performed by introducing an appropriate hydrophilic group into the Ph or 2-pyridyl ring. Thus, the 1-(6-aminopyridin-2-ylmethyl)piperidine analog I (R = 6-amino-2-

L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

pyridylmethyl) exhibiting 190-fold selectivity for M3 receptors (Ki = 2.8 nM) over M2 receptors (Ki = 530 nM) in a human binding assay and good in vitro metabolic stability in dog and human hepatic microsomes was identified. This compd. has excellent oral activity at 4 h after oral dosing (1 mg/kg), inhibiting methacholine-induced bronchoconstriction in dogs, and may be useful in clin. situations in which M3 over M2 selectivity is desirable.

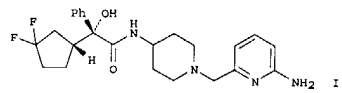
AN 2000:832187 CAPLUS
DN 134:147471
TI A potent, long-acting, orally active (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide: a novel muscarinic M3 receptor antagonist with high selectivity for M3 over M2 receptors
AU Mitsuya, Morihiro; Kobayashi, Kensuke; Kawakami, Kumiko; Satoh, Atsushi; Ogino, Yoshio; Kakikawa, Taro; Ohtake, Norikazu; Kimura, Toshifumi; Hirose, Hiroyasu; Sato, Akio; Numazawa, Tomosige; Hasegawa, Takuro; Noguchi, Kazuhito; Mase, Toshiaki
CS Banyu Tsukuba Research Institute in Collaboration with Merck Research Laboratories, Tsukuba, Ibaraki, 300-2611, Japan
SO Journal of Medicinal Chemistry (2000), 43(26), 5017-5029
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
IT **203321-88-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and muscarinic receptor antagonist activity of cyclopentylphenylacetamide derive.)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

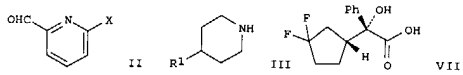


RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

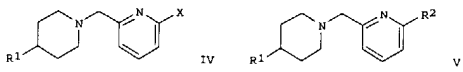
L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II III VII



IV V

AB An industrial process for the preparation of the title compds. (I) or salts thereof is characterized by reacting a compound of general formula (II; X = halo) or a salt thereof with a compound of general formula (III; R1 = optionally protected amino) or a salt thereof under reducing conditions to obtain a compound of general formula (IV; X, R1 = same as above) or salts thereof, reacting this compound or this salt with an aminating agent to obtain a compound of general formula (V; R2 = optionally protected amino) or a salt thereof, freeing at need the compound V or the salt thereof from the amino-protecting group of R1 and the amino substituent of R2 to obtain compound V (R2 = NH2) (VI) or a salt thereof, condensing the compound V or VI or the salt thereof with compound (VII), and removing the substituent of R2. This process gives in high yields and fewer steps I which is known to exhibit highly selective antagonism against muscarine M3 receptor and to be useful for the treatment or prevention of respiratory, urinary, or digestive tract diseases (no data).

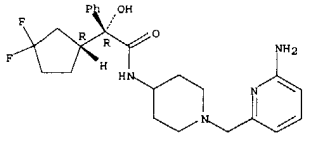
AN 2000:790497 CAPLUS
DN 133:350147
TI Processes for the preparation of piperidylmethylpyridine derivatives
IN Nemoto, Takayuki; Kawasaki, Masashi; Itoh, Takahiro; Mase, Toshiaki
PA Banyu Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA Japanese

L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2000066579 | A1 | 20001109 | WO 2000-JP2755 | 20000426 |
| | W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| PRAI | JP 1999-123157 | A | 19990428 | | |

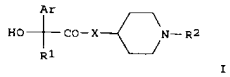
OS CASREACT 133:350147; MARPAT 133:350147
IT **203321-88-4P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process or preparation of piperidylmethylpyridine derivs. as muscarine M3 receptor antagonists)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2 pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

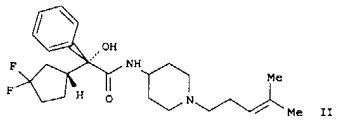


RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II

AB The title compds. (I; Ar = (un)substituted aryl or heteroaryl etc.; R1 = C1-3 cycloalkyl in which 1-4 arbitrary H may be substituted by F; R2 = saturated or unsatd., aliphatic C5-15 hydrocarbyl in which 1-6 arbitrary H may be
substituted by F, aralkyl, arylalkenyl, or heteroarylalkyl or heteroarylalkenyl having 1-2 heteroatoms selected from the group consisting of N, O, S; X = O, NH) or pharmaceutically acceptable salts thereof are prepared Because of having selective muscarinic receptor antagonism and being excellent in oral activity, persistence of the action
and dynamic in vivo, I are useful as efficacious and safe remedies or preventives with little side effects for respiratory, urol. and digestive diseases. Thus, (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid (preparation given) was reacted with 4-amino-1-(4-methyl-3-pentenyl)piperidine (preparation given) in the presence of 1,1'-carbonyldiimidazole and 4-dimethylaminopyridine to give the title compound
(II), which showed ED50 of 0.033 mg/Kg against muscarinic receptor antagonism when tested with rat.
AN 1998:112344 CAPLUS
DN 128:192550
TI Preparation of fluorinated 1,4-disubstituted piperidine derivatives as muscarinic receptor antagonists
IN Tsuchiya, Yoshimi; Nomoto, Takashi; Ohsawa, Hirokazu; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PA Banyu Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

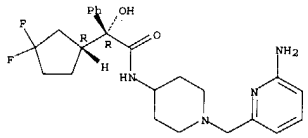
L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9805641 | A1 | 19980212 | WO 1997-JP2600 | 19970728 |
| | W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2261680 | AA | 19980212 | CA 1997-2261680 | 19970728 |
| | AU 9736351 | A1 | 19980225 | AU 1997-36351 | 19970728 |
| | AU 716050 | B2 | 20000217 | | |
| | EP 930298 | A1 | 19990721 | EP 1997-933037 | 19970728 |
| | EP 930298 | B1 | 20021218 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | BR 9711108 | A | 19990817 | BR 1997-11108 | 19970728 |
| | CN 1226588 | A | 19990825 | CN 1997-196911 | 19970728 |
| | TR 9900204 | T2 | 20000121 | TR 1999-9900204 | 19970728 |
| | JP 2000169449 | A2 | 20000620 | JP 2000-27462 | 19970728 |
| | JP 3282618 | B2 | 20020520 | | |
| | JP 2000178231 | A2 | 20000627 | JP 2000-27461 | 19970728 |
| | JP 3282617 | B2 | 20020520 | | |
| | JP 3063164 | B2 | 20000712 | JP 1998-507794 | 19970728 |
| | TR 200001482 | T2 | 20001121 | TR 2000-200001482 | 19970728 |
| | NZ 333842 | A | 20010525 | NZ 1997-333842 | 19970728 |
| | AT 229941 | E | 20030115 | AT 1997-933037 | 19970728 |
| | ES 2188961 | T3 | 20030701 | ES 1997-933037 | 19970728 |
| | US 5948792 | A | 19990907 | US 1997-903768 | 19970731 |
| | ZA 9706813 | A | 19980211 | ZA 1997-6813 | 19970831 |
| | KR 2000022214 | A | 20000425 | KR 1998-710633 | 19981224 |
| | NO 9900472 | A | 19990201 | NO 1999-472 | 19990201 |
| | US 6040449 | A | 20000321 | US 1999-290607 | 19990413 |
| PRAI | JP 1996-219436 | A | 19960801 | | |
| | JP 1997-53979 | A | 19970221 | | |
| | JP 1998-507794 | A3 | 19970728 | | |
| | WO 1997-JP2600 | W | 19970728 | | |
| | US 1997 903768 | A3 | 19970731 | | |

OS MARPAT 128:192550
IT **203321-30-6P 203321-31-7P 203321-42-0P 203321-45-3P 203321-51-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of fluorinated 1,4-disubstituted piperidine derivs. as muscarinic receptor antagonists)
RN 203321-30-6 CAPLUS
CN Benzeneacetamide, N-[1-[(6 amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(3,3-difluorocyclopentyl)-α-hydroxy-, dihydrochloride, [R (R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

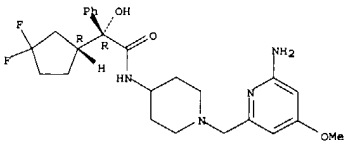
L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



●2 HCl

RN 203321-31-7 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-4-methoxy-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α hydroxy-, dihydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

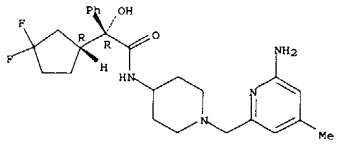
Absolute stereochemistry.



●2 HCl

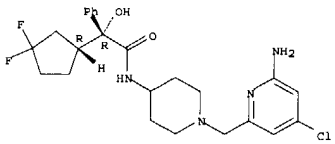
RN 203321-42-0 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-4-methyl-2-pyridinyl)methyl]-4-piperidinyl]-α (3,3-difluorocyclopentyl) α-hydroxy-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



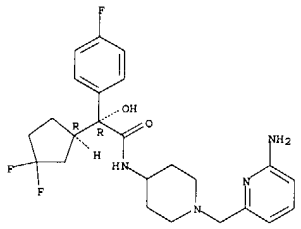
L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
RN 203321-45-3 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-4-chloro-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl) α-hydroxy-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 203321-51-1 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl) 4-fluoro-α-hydroxy-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

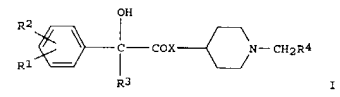
Absolute stereochemistry.



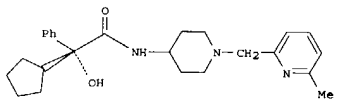
IT **203321-88-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of fluorinated 1,4-disubstituted piperidine derivs. as muscarinic receptor antagonists)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



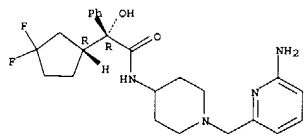
II

AB Substituted heteroarom. derivs. I [R1 and R2 are the same or different and each represents hydrogen, halogeno or lower alkyl; R3 represents C3-6 cycloalkyl or cycloalkenyl; R4 represents heteroaryl having one or two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur atoms which may be fused with the benzene ring, provided that the heteroaryl is optionally substituted by lower alkyl, halogeno, lower alkoxy, amino or hydroxymethyl; and X represents O or NH] are prepared. The compds. are useful for the treatment of respiratory diseases (asthma, chronic respiratory obstruction, pulmonary fibrosis, etc.), urol. diseases accompanied by urination disorders (frequent urination, urgency or micturition, urinary incontinence, etc.) and digestive diseases. In an in vitro test for tracheal M3 receptor antagonism, the title compound II (preparation given) showed the KB value of 4.4 nM.
AN 1997:369690 CAPLUS
DN 126:343498
TI Preparation of substituted heteroaromatic derivatives as selective M3 muscarinic antagonists
IN Mase, Toshiaki; Mitsuya, Morihiro; Kobayashi, Kensuke; Noguchi, Kazuhito
PA Banyu Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9713766 | A1 | 19970417 | WO 1996-JP2904 | 19961007 |
| | W: AU, CA, CN, JP, KR, US | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | CA 2234619 | AA | 19970417 | CA 1996-2234619 | 19961007 |



L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



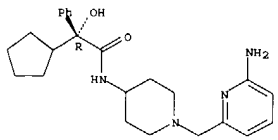
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

| | | | | | |
|---|---|---|---|---|---|
| | AU 9671459 | A1 | 19970430 | AU 1996-71459 | 19961007 |
| | EP 863141 | A1 | 19980909 | EP 1996-932827 | 19961007 |
| | EP 863141 | B1 | 20010912 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | AT 205490 | E | 20010915 | AT 1996-932827 | 19961007 |
| | US 6130232 | A | 20001010 | US 1998-51287 | 19980409 |
| PRAI | JP 1995-291716 | A | 19951013 | | |
| | JP 1995-351342 | A | 19951226 | | |
| | WO 1996-JP2904 | W | 19961007 | | |

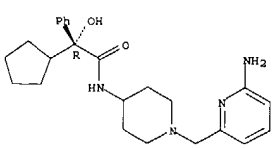
OS MARPAT 126:343498
IT **189819-56-5P 189819-57-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted heteroarom. derivs. as selective M3 muscarinic antagonists)
RN 189819-56-5 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-cyclopentyl-α-hydroxy , (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 189819-57-6 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-cyclopentyl-α-hydroxy-, dihydrochloride, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

9/29/04

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=> file uspatall
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       116.00     271.63

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                       -16.80     -16.80

FILE 'USPATFULL' ENTERED AT 14:32:54 ON 29 SEP 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 14:32:54 ON 29 SEP 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his

     (FILE 'HOME' ENTERED AT 14:29:44 ON 29 SEP 2004)

     FILE 'REGISTRY' ENTERED AT 14:29:53 ON 29 SEP 2004
L1                STRUCTURE UPLOADED
L2             0 S L1
L3            14 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 14:30:22 ON 29 SEP 2004
L4            24 S L3

     FILE 'USPATFULL, USPAT2' ENTERED AT 14:32:54 ON 29 SEP 2004

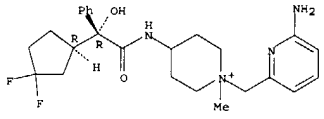
=> s l3
L5             6 L3

=> d abs bib fhitstr 1-6
```

L5 ANSWER 1 OF 6 USPATFULL on STN
AB The invention features quaternary ammonium compounds of formula I, described herein, and their use in treating asthma, chronic obstructive pulmonary disorder, allergic rhinitis, and infectious rhinitis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2004:172610 USPATFULL
TI Quaternary ammonium compounds
IN Heath, Timothy Gordon, Wildwood, MO, UNITED STATES
PI US 2004132774 A1 20040708
AI US 2003-688348 A1 20031017 (10)
PRAI US 2002-421962P 20021029 (60)
DT Utility
FS APPLICATION
LREP PHARMACIA & UPJOHN, 301 HENRIETTA ST, 0228-32-LAW, KALAMAZOO, MI, 49007
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **688320-38-9P**
(muscarinic receptor antagonist; preparation of quaternary ammonium compds., in particular piperidinium derivs., as muscarinic receptor antagonists)
RN 688320-38-9 USPATFULL
CN Piperidinium, 1-[(6-amino-2-pyridinyl)methyl]-4-[[(2R)-[(1R)-3,3-difluorocyclopentyl]hydroxyphenylacetyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

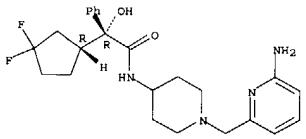


● I⁻

L5 ANSWER 2 OF 6 USPATFULL on STN
AB An improved and efficient synthesis for the preparation of 2-amino-6-[(4-aminopiperidin-1-yl]methyl]pyridine, an intermediate compound in the preparation of muscarinic M3 receptor antagonists, includes as a final step the removal of trimethylacetyl and an amino protecting group from 2-trimethylacetyl-amino-6-[(4-protected aminopiperidin-1-yl)methyl]pyridine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2001:229774 USPATFULL
TI Process for the preparation of chemical compounds
IN Maligres, Peter E., Fanwood, NJ, United States
Lee, Jaemoon, Edison, NJ, United States
PI US 2001051727 A1 20011213
US 6469172 B2 20021022
AI US 2001-799440 A1 20010305 (9)
PRAI US 2000-187816P 20000308 (60)
DT Utility
FS APPLICATION
LREP MERCK AND CO INC, P O BOX 2000, RAHWAY, NJ, 070650907
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 605
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **203321-88-4P**
(preparation of piperidine derive.)
RN 203321-88-4 USPATFULL
CN Benzeneacetamide, N-[1 [(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



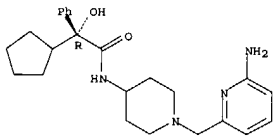
L5 ANSWER 3 OF 6 USPATFULL on STN
AB This invention provides substituted heteroaromatic ring derivatives which are represented by a general formula [I] below: ##STR1## [in the formula, R.sup.1 and R.sup.2 may be same or different and each signifies hydrogen, halogen or lower alkyl; R.sup.3 signifies C.sub.3 -C.sub.6 cycloalkyl or cycloalkenyl; R.sup.4 signifies a heteroaromatic ring group which may be condensed with a benzene ring and which has 1 or 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur atoms (said heteroaromatic ring group being optionally substituted with lower alkyl, halogen, lower alkoxy, amino or hydroxymethyl); and X stands for O or NH]

or their pharmaceutically acceptable salts.

The substituted heteroaromatic ring derivatives of the present invention have selective M.sub.3 muscarinic receptor antagonist activity, and hence they are useful as therapeutic or prophylactic agents which are safe and efficacious with little side effects, of respiratory diseases such as asthma, chronic airway obstruction and pulmonary fibrosis, etc.; urinary diseases which induce such urination disorders as pollakiurea, urgency and urinary incontinence, etc.; and gastrointestinal diseases such as irritable bowel syndrome, spasm of gastrointestinal tract and gastrointestinal hyperkinesia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AN 2000:134899 USPATFULL
TI Substituted piperidine derivatives as muscarinic M.sub.3 receptor antagonists
IN Mase, Toshiaki, Tsukuba, Japan
Mitsuya, Morihiro, Tsukuba, Japan
Kobayashi, Kensuke, Tsukuba, Japan
Noguchi, Kazuhito, Tsukuba, Japan
PA Banyu Pharmaceutical Coaltd, Tokyo, Japan (non-U.S. corporation)
PI US 6130232 20001010
WO 9713766 19970417
AI US 1998-51287 19980409 (9)
WO 1996-JP2904 19961007
19980409 PCT 371 date
19980409 PCT 102(e) date
PRAI JP 1995-291716 19951013
JP 1995-351342 19951226
DT Utility
FS Granted
EXNAM Primary Examiner: Chang, Ceila
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1288
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **189819-56-5P**
(preparation of substituted heteroarom. derivs. as selective M3 muscarinic antagonists)
RN 189819-56-5 USPATFULL
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α cyclopentyl-α-hydroxy-, (R)- (9CI) (CA INDEX NAME)

L5 ANSWER 3 OF 6 USPATFULL on STN (Continued)
Absolute stereochemistry.



L5 ANSWER 4 OF 6 USPATFULL on STN

AB In the production of fluorine-containing 1,4-disubstituted piperidine derivatives by the reaction of a carboxylic acid of formula where Ar represents aryl or heteroaryl and R.sup.10 represents C.sub.3 -C.sub.6 cycloalkyl in which up to 4 hydrogen atoms are substituted with fluorine or C.sub.3 -C.sub.6 cycloalkyl having 1 to 2 protected or unprotected hydroxyl or oxo groups, or a reactive derivative thereof, with a piperidine derivative of formula [IV] as defined in the specification, especially useful results are obtained using 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine or a salt thereof, e.g., trihydrochloride, as the piperidine derivative.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AN 2000:34693 USPATFULL

TI Fluorine-containing 1, 4-disubstituted piperidine derivatives

IN Tsuchiya, Yoshimi, Tsukuba, Japan
Nomoto, Takashi, Menuma-machi, Japan
Ohsawa, Hirokazu, Tsukuba, Japan
Kawakami, Kumiko, Tsukuba, Japan
Ohwaki, Kenji, Tsukuba, Japan
Nishikibe, Masaru, Tsukuba, Japan

PA Banyu Pharmaceutical Co Ltd, Tokyo, Japan (non-U.S. corporation)

PI US 6040449 20000321

AI US 1999-290607 19990413 (9)

RLI Division of Ser. No. US 1997-903768, filed on 31 Jul 1997, now patented, Pat. No. US 5948792

PRAI JP 1996-219436 19960801
JP 1997-53979 19970221

DT Utility

FS Granted

EXNAM Primary Examiner: Chang, Ceila

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2481

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

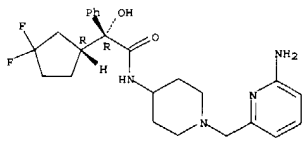
IT **203321-30-6P**
(preparation of fluorinated 1,4-disubstituted piperidine derivs. as muscarinic receptor antagonists)

RN 203321-30-6 USPATFULL

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α-hydroxy-, dihydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L5 ANSWER 4 OF 6 USPATFULL on STN (Continued)



●2 HCl

L5 ANSWER 5 OF 6 USPATFULL on STN

AB Novel fluorine-containing 1,4-disubstituted piperidine derivatives, represented by general formula [I] ##STR1## such as, for example, (2R) N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide or pharmaceutically acceptable salt thereof, are potent and selective antagonists for muscarinic M.sub.3 receptors with little side effects. The compounds of formula [I] exhibit excellent oral activity, duration of activity and pharmacolkinetics. They are useful for treatment and prophylaxis of respiratory diseases, such as chronic obstructive pulmonary diseases; urinary diseases, such as urinary incontinence; and digestive diseases, such as irritable bowel syndrome, and motion sickness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AN 1999:106468 USPATFULL

TI Fluorine containing 1,4-disubstituted piperidine derivatives

IN Tsuchiya, Yoshimi, Tsukuba, Japan
Nomoto, Takashi, Menuma-machi, Japan
Ohsawa, Hirokazu, Tsukuba, Japan
Kawakami, Kumiko, Tsukuba, Japan
Ohwaki, Kenji, Tsukuba, Japan
Nishikibe, Masaru, Tsukuba, Japan

PA Banyu Pharmaceutical Co., Ltd., Tokyo, Japan (non U.S. corporation)

PI US 5948792 19990907

AI US 1997-903768 19970731 (8)

PRAI JP 1996-219436 19960801
JP 1997-53979 19970221

DT Utility

FS Granted

EXNAM Primary Examiner: Chang, Ceila

LREP Sherman and Shalloway

CLMN Number of Claims: 23

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2821

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

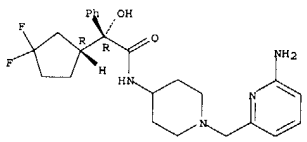
IT **203321-30-6P**
(preparation of fluorinated 1,4-disubstituted piperidine derivs. as muscarinic receptor antagonists)

RN 203321-30-6 USPATFULL

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α-hydroxy-, dihydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L5 ANSWER 5 OF 6 USPATFULL on STN (Continued)



●2 HCl

L5 ANSWER 6 OF 6 USPAT2 on STN

AB An improved and efficient synthesis for the preparation of 2-amino-6-[(4-aminopiperidin-1-yl)methyl]pyridine, an intermediate compound in the preparation of muscarinic M3 receptor antagonists, includes as a final step the removal of trimethylacetyl and an amino protecting group from 2-trimethylacetyl-amino-6-[(4-protected aminopiperidin-1-yl)methyl]pyridine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AN 2001:229774 USPAT2

TI Process for the preparation of chemical compounds

IN Maligres, Peter E., Fanwood, NJ, United States
Lee, Jaemoon, Edison, NJ, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 6469172 B2 20021022

AI US 2001-799440 20010305 (9)

PRAI US 2000-187816P 20000308 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Covington, Raymond

LREP Yang, Mollie M., Rose, David L.

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)

LN.CNT 614

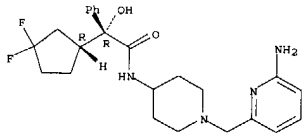
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **203321-88-4P**
(preparation of piperidine derivs.)

RN 203321-88-4 USPAT2

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 35.30 | 306.93 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -16.80 |

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